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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/281,674	03/30/99	BUJARD H	BBI-013C3CN2

000959
LAHIVE & COCKFIELD
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HM12/0828

EXAMINER	
SHUKLA,R	
ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 08/28/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/281,674	Applicant(s) BUJARD ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-14 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9-14 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *30 March 1999* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The request filed on 6-25-01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/281674 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 1-6, 9-14, 17-19 are under consideration in the instant application.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claim 1-6, 9-14, and 17-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. U.S. Patent No. 5,888,981, for reasons of record set forth in the previous office action of 5-23-00. Although the conflicting claims are not identical, they are not patentably distinct from each other because the invention of the instant application can not be practiced without infringing on the invention of the cited patent.

5. Claims 1-6, 9-14, and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of

regulating expression of a tet operator-linked gene in a cell, wherein a first nucleic acid molecule comprises the tet-operator linked gene whereas a second nucleic acid nucleic acid encodes a tetracycline-controllable transactivator tTA which comprises a Tet repressor operably linked to a polypeptide which directly or indirectly activates transcription in eukaryotic cells, wherein the method is carried out in a cell in vitro or in vivo wherein both the nucleic acids are administered directly to the cell, or an ex vivo method wherein both the nucleic acids are introduced in a cell and the cell is administered to a subject, does not reasonably provide enablement for the claimed wherein the cell is present in a subject in vivo and one or both the nucleic acids are administered by different methods or wherein cells have integrated one nucleic acid in the genome at a site or at randomly and the second nucleic acid is administered by any method or a method wherein the first nucleic acid is present in a cell, the cell is administered to a subject and the second nucleic acid is administered to the subject by any method or any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

As instantly recited claimed invention encompasses a method of regulating expression of a tet operator-linked gene in a cell, wherein a first nucleic acid molecule comprises the tet-operator linked gene whereas a second nucleic acid nucleic acid encodes a tetracycline-controllable transactivator tTA which comprises a Tet repressor operably linked to a polypeptide which directly or indirectly activates transcription in eukaryotic cells, wherein the method is carried out (i) in a cell in vitro or in vivo wherein both the nucleic acids are administered directly to the cell (ii) an ex vivo method wherein both the nucleic acids are introduced in a cell in vitro and the cell is administered to a subject (iii) the cell is present in a subject in vivo and one or both the nucleic acids are administered by different methods (iv) wherein cells have integrated one nucleic acid in the genome at a site or at randomly and the second nucleic acid is administered by any method and (v) a method wherein the first nucleic acid is present in a cell, the cell is administered to a subject and the second nucleic acid is administered to the subject by any method.

However, claimed invention is not enabled commensurate with the scope of the claims because the method of targeted expression of a nucleic acid is highly unpredictable and the specification as filed does not provide sufficient guidance as to how an artisan of skill would have had practiced the claimed invention without undue experimentation.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

It is noted that for practicing the instantly claimed invention, an artisan have to be able to deliver the two nucleic acids to the same cell so that the tTA protein is produced from the second nucleic and the tTA should be able to interact with the tTA responsive promoter and therefore, induce the expression of the gene that is operably linked to tet-operator in the first nucleic acid. In the instant case, the first nucleic acid may be present in any cell of a subject, for example, integrated into the genome of the cell. If one had to administer the second nucleic acid to the subject by different routes, the question is: would the second nucleic acid reach the targeted cell (which comprises the first nucleic acid)?. The art of targeting

expression of a polynucleotide to a particular cell or tissue is unpredictable. Numerous factors complicate the gene delivery art which would not have been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used and the protein being produced. In the instant case, claims recite a nucleic acid which would mean it could be a naked DNA or a plasmid or a vector. While progress has been made in recent years in the area of *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al (FASEB J. 9:190-199, 1995) discussed the state of the art of targeted vectors for gene therapy and noted that there is requirement to produce vector systems that can deliver therapeutic genes to the appropriate target cells in vivo or ex vivo and that that these systems should be efficient and accurate. They further stressed that the range of different diseases means that no single delivery system is likely to be universally acceptable and that the stringency with which the therapeutic genes need to be accurately delivered could greatly vary, for example, a vector system used for gene delivery in cystic fibrosis tissue would not be suitable for cancer gene therapy (see first paragraph in column 1 on page 190). Likewise, Deonarain (Deonarain MP. Exp. Opin. Ther. Patents. 8:53-69, 1998) also noted that gene delivery remains the major technological stumbling block in gene therapy strategies. Deonarain further noted that there are several drawbacks of different targeting vectors, such as, risk of secondary malignancies due to integrated vectors, recombination of disabled viruses to produce infective virus, lack of cell specificity, lack of infection of non-dividing cells by retrovirus, inactivation and inactivation of the viral vectors by host complement (see column 1 continued in

column 2 on page 54). Even if one had to assume the two nucleic acids would have reached the same cell, one would not be certain whether sufficient amount of tTA would have been produced that would induce gene expression. In view of the unpredictability of the targeted gene delivery, an artisan of skill would have to carry out extensive experimentation to figure out conditions that would have allowed targeted deliveries of both the nucleic acids to the same cells and such experimentation would have been considered undue because such experimentation would not have been routine.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of skill in the art at the time of the invention would have required an undue amount of experimentation to practice the claimed invention. Accordingly, limitation of the scope of the claimed invention to a method of regulating expression of a tet operator-linked gene in a cell, wherein a first nucleic acid molecule comprises the tet-operator linked gene whereas a second nucleic acid nucleic acid encodes a tetracycline-controllable transactivator tTA which comprises a Tet repressor operably linked to a polypeptide which directly or indirectly activates transcription in eukaryotic cells, wherein the method is carried out in a cell in vitro or in vivo wherein both the nucleic acids are administered directly to the cell, or an ex vivo method wherein both the nucleic acids are introduced in a cell and the cell is administered to a subject, is proper.

6. No claim is allowed.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is

(703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER